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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/091,578	10/06/1998	EDWIN L. MADISON	19191.0002	5096

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EXAMINER	
SCHWADRON, RONALD B	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/091,578	MADISON ET AL.	
	Examiner	Art Unit	
	Ron Schwadron, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 68-89 is/are pending in the application.

4a) Of the above claim(s) 73,76,79,83 and 85 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 68-72,74,75,77,78,80-82,84 and 86-89 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election of the species blood clot, αIIbβ3 and tPA in the reply filed on 4/26/2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is noted that in response to the restriction requirement enunciated 6/30/99 applicant had previously elected the species of thrombolytic agent/anticoagulant as a therapeutic or diagnostic functional entity, a CDR of an immunoglobulin as a specific peptide mimetic source, and specific protein or specific polyamino acid and integrin as a specific target

2. Claims 73,76,79,83,85 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/26/2004.

3. Claims 68-72,74,75,77,78,80-82,84,86-89 are under consideration.

4. The previously pending rejections are withdrawn in view of the newly submitted claims and applicants arguments.

5. The amendment to the specification filed 12/19/2003, line 4 recites "US 99/20577" wherein it should recite US 96/20577.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 68-72,74,75,77,78,80-82,84,86-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

There is no support in the specification as originally filed for the recitation of "retaining a specific binding characteristic for said target" in claim 68. The specification, page 12 states:

"A surface loop, as used in the claims, has retained one or more of its binding characteristics upon insertion into a non-native functional protein in a manner such that it remains as a surface loop, e.g., such that it replaces a removed surface loop in the non-native functional protein or such that it is inserted either between two regions of defined secondary structure in the non-native functional protein or between a domain of secondary structure and a terminus in the non-native functional protein.".

The instant limitation as used in claim 68 does not include the limitation that the surface loop *has retained one or more of its binding characteristics upon insertion into a non-native functional protein in a manner such that it remains as a surface loop, e.g., such that it replaces a removed surface loop in the non-native functional protein or such that it is inserted either between two regions of defined secondary structure in the non-native functional protein or between a domain of secondary structure and a terminus in the non-native functional protein.* The instant claims encompass a surface loop attached to the end of a molecule (eg. not inserted into a protein) and there is no disclosure in the specification as originally filed that a surface loop added to the end of a molecule would have the property of "retaining a specific binding characteristic for said target".

There is no support in the specification as originally filed for the recitation of "odorant or taste receptor" in claim 71. The specification, page 14 discloses "odorant or taste receptor" that are part of the seven membrane spanner protein family, but does not disclose such molecules without the aforementioned limitation (eg. that they are part of the seven membrane spanner protein family).

There is no support in the specification as originally filed for the recitation of "endothelial cells, smooth muscle cells" in claim 72. The specification, page 18 discloses "endothelial cells, smooth muscle cells" that are derived from the vasculature, but does not disclose such cells without the aforementioned limitation.

There is no support in the specification as originally filed for the recitation of "stem cells" in claim 72. The specification, page 18 discloses "stem cells" that are derived from bone marrow, but does not disclose such cells without the aforementioned limitation.

There is no support in the specification as originally filed for the scope of the claimed invention (eg. the claims constitute new matter for the reasons stated above).

8. The instant claims encompass a surface loop attached to the end of a molecule (eg. not inserted into a protein).

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 68,71,81,82,84,86 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolfson et al.

Wolfson et al. teach that the protease binding surface loop EAIPMSIPPE can be substituted into the cytokine interleukin-1β (see abstract and page 316, second column, *Discussion*, continued on next page). Wolfson et al. disclose that said loop maintains a specific binding characteristic (eg. it binds the appropriate protease (a protein enzyme), see abstract). Wolfson et al. indicate that the interleukin-1β would be expected to retain its binding specificity (see abstract, last sentence) and that the overall structure of the mutant is indistinguishable from wild type (see abstract), wherein said mutant protein has therefore retained a therapeutic property. The mutant protein is recombinantly prepared.

11. Claims 68-72,74,75,77,78,80-82,84,86 are rejected under 35 U.S.C. 102(b) as being anticipated by Maeda et al. as evidenced by Balint, Jr. (US Patent 5,075,423) and Barbas et al. (1993).

Maeda et al. teach insertion of RGDS peptide into truncated recombinant Protein A (see abstract). Said molecule constitutes a protein as per the definition of said word on page 12 of the specification. Protein A is recognized in the art as a therapeutic agent having a therapeutic property (for example see Balint, Jr., column 1, paragraphs 3 and 5). RGDS binds integrins (see page 15165, first column, last sentence). The RGD motif inherently binds αIIbβ3 integrin (see Barbas et al. page 10003, column 2. first incomplete paragraph) which is inherently found on the surface of platelets (see Barbas et al. page 10003, column 2. first incomplete paragraph) wherein platelets form blood clots. Maeda et al. disclose that the grafted RGDS forms a surface loop in the truncated protein A molecule (see page 15167, second column, last paragraph, continued on next page). Regarding claim 69, in view of the fact that the RGD motif is found in molecules that do not have cell adhesion activity (see page 15167, first column, last paragraph), the grafted peptide has been optimized to increase its natural affinity for target. The grafted RGDS peptide is functionally active and retains its binding specificity (see abstract) and the mutant truncated protein A retains a therapeutic property (eg. ability to bind IgG, see abstract). Protein A binds IgG wherein said molecule can occur on the surface of B cells.

12. Claims 68-72,74,75,77,78,80-82,84,86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quertermous et al. (US Patent 5,811,265) in view of Rodwell (US Patent 5,196,510) and Barbas et al.(1993).

The instant claims encompass a surface loop attached to the end of a molecule (eg. not inserted into a protein). Quertermous et al. teach tPA/antibody fragment recombinant conjugates (see abstract, column 2, second paragraph and column 7, fourth paragraph). Quertermous et al. do not teach that the conjugate contains the surface loop HCDR3 from Fab-9. Barbas et al. disclose Fab-9 monoclonal antibody wherein an optimized RGD peptide was inserted into HCDR3 (heavy chain CDR3) of said Fab (see pages 10004 and 10005). Barbas et al. teach that the inserted amino acid sequence mediates binding to the adhesion/adhesive protein integrin αIIbβ3 wherein said integrins are cell surface proteins found on platelets(see page 10006, first column) and wherein platelets are found in blood clots. Rodwell et al. teach that CDR3 peptides derived from an antibody with a particular specificity can be optimized for binding (see

column 24-25) and used in a conjugate to target the conjugate to a desired target (see columns 18-21). The HCDR3 of Barbas et al. has been optimized to increase its natural binding affinity (see column 2, page 10004). The integrin bound by the conjugate is a platelet cell surface protein. The integrin binds to the RGD motif found in Fab-9 CDR3 (see abstract). tPA is a thrombolytic agent (see column 2, second paragraph). It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Quertermous et al. teach tPA/antibody fragment recombinant conjugates whilst Barbas et al. disclose Fab-9 monoclonal antibody wherein an optimized RGD peptide was inserted into HCDR3 (heavy chain CDR3) of said Fab and that the inserted amino acid sequence mediates binding to the adhesion/adhesive protein integrin αIIbβ3 and Rodwell et al. teach that CDR3 peptides derived from an antibody with a particular specificity can be used in a conjugate to target the conjugate to a desired target (see columns 18-21). One of ordinary skill in the art would have been motivated to do the aforementioned because Barbas et al. teaches that the RGD motif can be used to bind a biomolecule to an integrin and the role of integrins in a variety of disease states whilst Rodwell et al. teach that CDR3 binding peptides derived from an antibody with a particular specificity can be used in a conjugate to target the conjugate to a desired target. In addition, Quertermous et al. teach tPA/antibody fragment recombinant conjugates and the potential uses of such conjugates (see abstract).

Regarding the Madison et al. declaration, the claims under consideration do not require insertion of a CDR into a foreign molecule. Rodwell et al. teach that CDR3 binding peptides derived from an antibody with a particular specificity can be used in a conjugate to target the conjugate to a desired target. Rodwell et al. teach such CDR3 peptide conjugates bind the antigen recognized by the CDR3 peptide (see Examples columns 24-31).

13. No claim is allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron, Ph.D. whose telephone number is 571 272-0851. The examiner can normally be reached on Monday to Thursday from 7:30am to 6:00pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at 571 272 0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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